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Research Paper

A New Nonlinear Autoregressive Exogenous (NARX)-based Intra-spinal Stimulation Approach to Decode Brain Electrical Activity for Restoration of Leg Movement in Spinally-injured Rabbits

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ABSTRACT

Introduction: This study aimed at investigating the stimulation by intra-spinal signals decoded from electrocorticography (ECoG) assessments to restore the movements of the leg in an animal model of spinal cord injury (SCI).

Methods: The present work is comprised of three steps. First, ECoG signals and the associated leg joint changes (hip, knee, and ankle) in sedated healthy rabbits were recorded in different trials. Second, an appropriate set of intra-spinal electric stimuli was discovered to restore natural leg movements, using the three leg joint movements under a fuzzy-controlled strategy in spinally-injured rabbits under anesthesia. Third, a nonlinear autoregressive exogenous (NARX) neural network model was developed to produce appropriate intra-spinal stimulation developed from decoded ECoG information. The model was able to correlate the ECoG signal data to the intra-spinal stimulation data and finally, induced desired leg movements. In this study, leg movements were also developed from offline ECoG signals (deciphered from rabbits that were not injured) as well as online ECoG data (extracted from the same rabbit after SCI induction).

Results: Based on our data, the correlation coefficient was 0.74±0.15 and the normalized root means square error of the brain-spine interface was 0.22±0.10.

Conclusion: Overall, we found that using NARX, appropriate information from ECoG recordings can be extracted and used for the generation of proper intra-spinal electric stimulations for restoration of natural leg movements lost due to SCI.

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Highlights

• Using the fuzzy controller, movement fitted the natural leg movement of the healthy animals confirming a strong correlation between the acquired simulated movements' and natural movements data.

• The nonlinear autoregressive exogenous (NARX) neural interface was able to produce intra-spinal stimulations that matched electrocorticography (ECoG) signals' data at an acceptable level.

Plain Language Summary

This study aimed to design a NARX-based neural interface that extracts motor commands from the cerebral cortex and generates fuzzy-based intra-spinal stimulations to restore the leg movements in spinal cord injury animals. the results of the present study showed that the fuzzy-based intra-spinal stimulation and the developed NARX neural interface could restore leg movements. Using NARX, appropriate information from ECoG recordings can be extracted and used for the generation of proper intra-spinal electric stimulations for restoration of natural leg movements lost due to SCI.

1. Introduction

Spinal cord injury (SCI) prevents impulse transfer from the brain to motor muscles, causing permanent movement disability and subsequent atrophy in the paralyzed limb muscles (Duggan et al. 2016). Functional electrical stimulation through physiotherapy is regarded as an efficacious way of stimulating paralyzed organs' nerves and muscles (Hagen et al., 2015) and is used against muscle atrophy and joint stiffness development (Freund et al., 2011). Nevertheless, it helps patients to control the paralyzed limbs under the control of the brain. Thus, an approach that decodes the brain's electrical activities (based on intra-cortical local field potentials, electrocorticography (ECoG), electroencephalography (EEG)) (Ragnarsson et al., 2008; Caldwell et al., 2019; Jackson et al., 2012), to produce appropriate electrical stimuli, could potentially restore arbitrary/intentional movements. Using such an approach, the affected region of the spinal cord can be bypassed to make the transfer of nerve impulses from the brain to the motor muscles possible.

For this purpose, several steps should be considered: firstly, the motor modules down the affected region of the spinal cord that controls the contraction of certain motor muscles should be identified (Bizzi et al., 2008) and then, appropriate electric stimuli should be deciphered.

In our previous study, to reveal motor modules in the spinal cord of anesthetized SCI rabbits, we aimed at restoration of SCI animal leg movements by intra-spinal stimulation based on a manual open-loop method (trial and error stimulation) (Younessi Heravi et al. ,2020). Since the trial-and-error approach is a tedious not-efficient approach to produce stimulation patterns, a close-loop computerized control strategy instead of a trial-and-error process for module stimulation could potentially improve the results and enhance leg restoration outcomes. One of the simplest and most functional methods for movement control based on intra-spinal electric stimulation is the fuzzy control method, which produces a proper set of electrical stimuli to induce natural movements of the limb (Roshani et al., 2013). The system demonstrated great success for this purpose and it could restore natural movements through intra-spinal electric stimulation (Asadi et al., 2012).

How to relate the brain electrical activity impulses (extracted from ECoG data) with the intra-spinal stimulation signals, is the key point in the recovery of a paralyzed limb. In recent years, many studies have been performed on brain signal decoding. In many of these approaches, attempts have been made to record the signals in animal models based on training, and then to restore physical activities, such as lower limb movements and upper limb movements (Bonizzato et al, 2018; Capogrosso et al., 2016; Samejima et al., 2021). The development of these studies on humans has also been limited (Ajiboye et al., 2018; Wagner et al., 2018). There are different linear techniques in online brain decoding, like partial least square regression (Foodeh et al., 2020; Shin et al., 2012), sparse linear regression (Heravi et al., 2020), and Kalman filtering (Asgharpour et al., 2020; Malik et al., 2010). In another previous study done by Heravi et al. (Heravi et al., 2020), a SLiR-based brain-spine interface was developed to decode intra-spinal stimulation from ECoG signals.

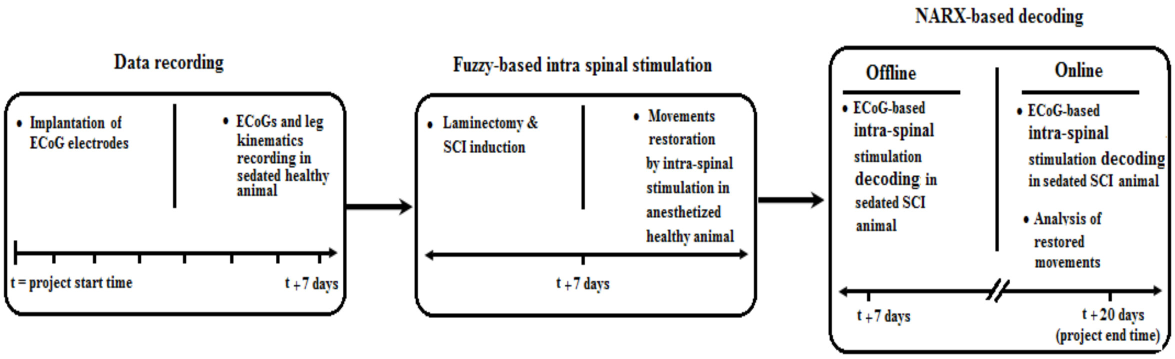

Figure 1. The block diagram explaining different parts of the project.

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Since the brain-spine system has a nonlinear dynamic nature, a powerful nonlinear dynamic system should be employed to model it. In this regard, using dynamic nonlinear computer-based algorithms may help to reveal relationships between brain electrical activity and intra-spinal electrical stimuli to induce intentional movements of a paralyzed limb (Hatsopoulos et al., 2009; Shakibaee et al., 2019). The nonlinear autoregressive exogenous (NARX) neural network model is one of these approaches that can be used for the dynamic neuromuscular systems associating the neural impulses with limb kinetics (Liu et al., 2017). Using this dynamic and nonlinear system, decoding intra-spinal stimulation from the ECoG data could be executed. As far as our literature survey showed, the current study is the first that used a nonlinear technique for the restoration of leg movements in rabbits under anesthesia.

Two major issues that exist in the restoration of the function of a paralyzed motor through the use of intra-spinal stimulation are (1) the production of appropriate patterns for electrical stimulations that lead to the restoration of movements and (2) the development of a neural interface to decode electrical stimulation patterns from ECoG information.

Here, we aimed to introduce and assess the efficacy of a new approach to bypass SCI using NARX and the fuzzy control system as the interface between the ECoG signals and intra-spinal electric stimuli, to induce leg movement in rabbits with SCI.

2. Materials and Methods

All animal procedures were done at the School of Medicine North Khorasan University of Medical Sciences, Bojnurd, Iran, based on the national guidelines for in vivo experimentation. Figure 1 shows the block diagram explaining different parts of the study. The relationship between the leg movement-related brain activity and the relevant electrical intra-spinal stimulation was achieved in three steps using three male Dutch rabbits (1.63±0.25 kg, 3.8±0.55 months old) with SCI. To this end, the brain's (cerebral cortex) electrical activity was first recorded along with the spontaneous leg movements (Figure 2 A). Then, the best possible spinal cord-stimulating pulse patterns fitting spontaneous movements were determined by a fuzzy controller, which was a homemade program comparing the spontaneous data with the data achieved from the same animals after SCI induction (Figure 2 B). Finally, the relationship between ECoG data and the optimum pulse was attained by a nonlinear autoregressive exogenous (NARX) model (Figure 2 C).

Simultaneous ECoG and leg kinematics in a sedated healthy animal

To record ECoG, four custom-made tungsten electrodes (0.40 mm in diameter) were inserted into the cerebral cortex of the rabbits that were anesthetized by ketamine (35 mg/kg)/xylazine (5 mg/kg). Next, four holes were made into the skull (bregma region) and electrodes were implanted through these holes and fixed (Figure 2 A). Seven days later, sedation was induced by chloroform exposure for a few seconds, to indicate their fast activity. The rabbits were held in a position, in which they only had free movements of the leg. To analyze leg kinematics, the hip, knee, and ankle joints of the right leg were colored in blue and three typical rabbit leg movements on sedate condition (i.e. pushing the leg toward the back, pulling the leg into the abdomen, and pushing the leg forward), were recorded by employing a digital camera (at 50 frames/sec). Using a homemade program in Microsoft visual studio C#, the real-time joint angle changes were monitored. Concurrently, the corresponding ECoG was recorded using the PowerLab system (sampling frequency 500 Hz) (AD Instrumentation. Co, Australia). Under sedation, ECoG signals and related

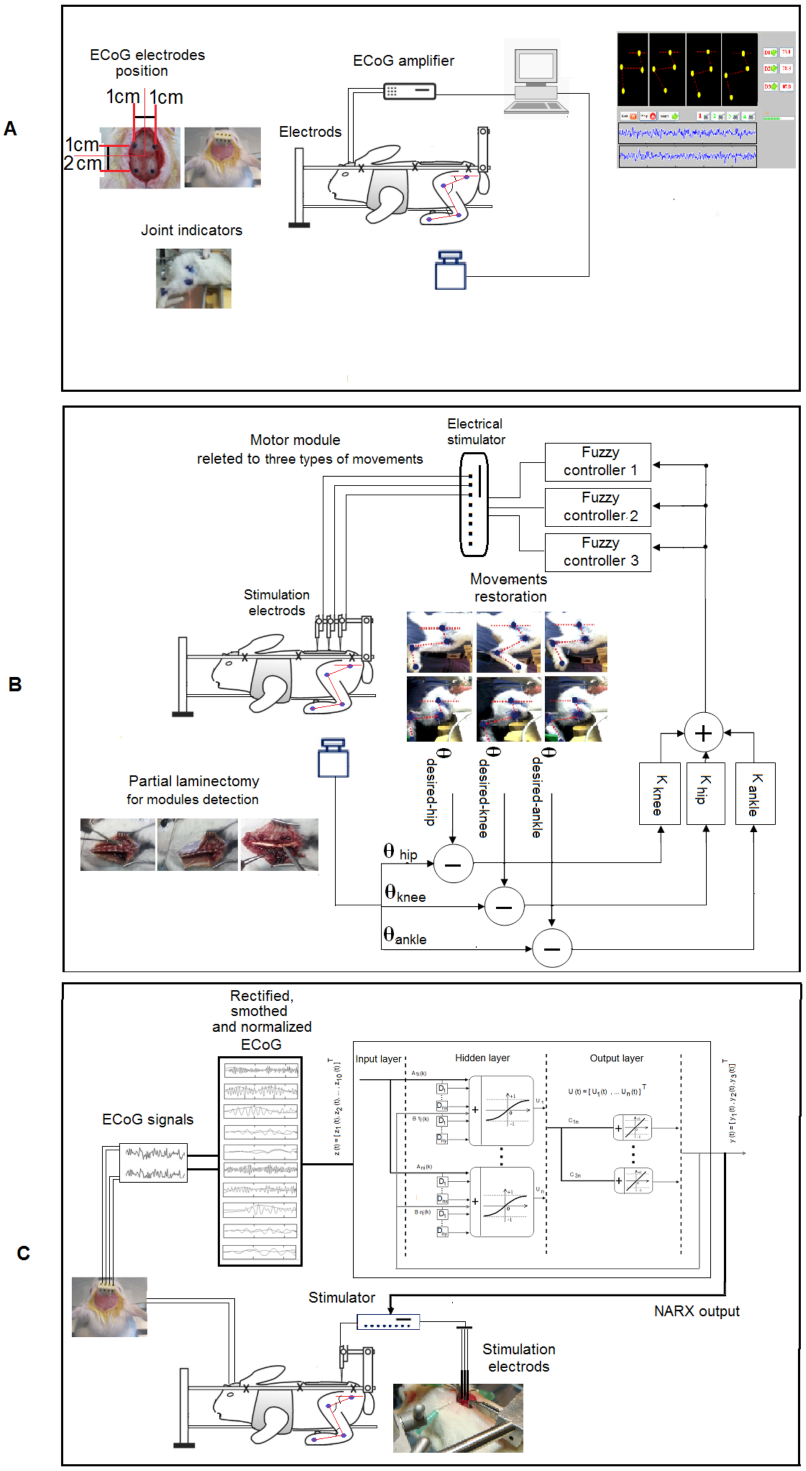

Figure 2. The experimental setup

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A) One pair of electrodes was implanted +1.0 cm from the bregma and 2 cm lateral to the midline, and another pair was implanted -1.0 cm from the bregma and 2 cm lateral to the midline. A ground electrode consisting of a free wire was placed under the neck's skin. Hip, knee, and ankle joint angles were calculated by C#.Net software based on the blue indicator;

B) A partial laminectomy was performed to damage the spinal cord (i.e. to induce SCI), and then, motor modules related to three types of movements were detected. For controlling each module, a fuzzy controller was designed to restore the movements. The joint angle error was considered as the input of each controller;

C) Final ECoG data were applied as inputs of the NARX model and the outputs of the model were intra-spinal stimulations delivered to electrodes in spinal modules.

joint angles of the leg were recorded 40 times for each leg movement.

Intra-spinal cord stimulation based on the Fuzzy control strategy in an SCI model

After leg kinematics analysis, motor modules were spotted by a trial-and-error approach on the spinal cord-based three electrodes (silver, 0.04 mm thickness, A-M Systems, USA) and a custom-made stimulator (Heravi et al., 2019). The configuration of the proposed control strategy is schematically depicted in Figure 2 B. For controlling each module, a controller was designed to restore each movement. Each controller has a stimulation signal (monophasic pulse, width=0.5 ms, amplitude=100 to 200 µA, and frequency=50 Hz) as an output, which is delivered to the module of the spinal cord via the implanted electrode. For each controller, 25 sets of "if… then…" were considered as a rule base. The output of fuzzy control was calculated by the fuzzy rule base, Mamdani method, Gaussian membership functions, and centroid defuzzification as previously shown (Heravi et al., 2019). In the proposed fuzzy control, fuzzy sets consist of negative big (NB), negative small (NS), zero (Z), positive small (PS), positive medium (PM), and positive big (PB) (Kovacic et al., 2018, Roshani et al., 2013). The movement-triggered delay after stimulation (i.e. constant time delay), was experimentally estimated. This time delay was approximately 200 ms. Joint angles recorded before SCI induction were compared with joint angles recorded after SCI induced by a combination of three fuzzy controllers output. By calculation of normalized root mean square (NRMS) error, the error tracking was assessed using Equation 1:

$$1.\ NRMS=\frac{\sqrt{\frac{\sum^{n}_{i=0}(y_i^p-y_i^a))^2}{n}}}{(y^a{}_{max}-y^a min)}$$

For each time point (i)), y_i^p,and are the joint angle before SCI and after stimulation. y^a_{max} and y^a_{min} are the maximum and minimum of the joint angle before SCI. The similarity of before-SCI joint angles and those recorded after intra-spinal stimulations induced by fuzzy controllers is reported as the correlation coefficient (CC).

Decoding intra-spinal stimulation from ECoGs

After finding the appropriate intra-spinal stimulation by fuzzy control strategy, a model was developed to relate the intra-spinal stimulation with the ECoG signal to restore the natural movements of the leg under brain order (Figure 2 C). To this end, firstly, the ECoG signals achieved in "Simultaneous ECoG and leg kinematics in sedated healthy animal" were preprocessed using the common average reference method (Chen et al., 2013, Ludwig et al., 2009). In this method, the signal values of four electrodes (each pair entered one channel), implanted in the cerebral cortex, were averaged, and then the values were subtracted from this mean for each channel. Then, each preprocessed signal was grouped into five frequency bands. The δ, θ, α, β, and γ bands ranged 0~4, 4~8, 8~14 Hz, 14~30, and 30~50 Hz, respectively (Shin et al. 2012). These data were digitally rectified and smoothed. Then, the signals were down-sampled from 500 to 50 Hz, i.e. from the sampling frequency of ECoG signal measurement to the sampling frequency of the intra-spinal stimulations (Younessi et al., 2020). Finally, each smoothed signal was normalized according to the z-score Equation 2:

$$2.\ z_i(t)=\frac{x_i(t)-\mu_i}{\sigma_i}\ i=(1\ to\ 2\times 5)$$

Where, i ranges from 1 to 10 (2 of ECoG channels * 5 of frequency bands), and denote the Mean±SD of $x_i(t)$. The $z_i(t)$ was the final ECoG data to be related to the intra-spinal stimulation signal's data achieved in " Intra-spinal cord stimulation based on the Fuzzy control strategy in an SCI model". The next step was to figure out how to convert the normalized data of ECoG to the appropriate intra-spinal stimulation data. This was done with the aid of the NARX neural network model, which dynamically converts ECoG data obtained over time to the relevant intra-spinal data with recurrent feedback from the spinal stimulation data. The NARX neural network is a nonlinear dynamic recurrent network that encloses several layers with feedback connections (Liu et al., 2017). Three NARX models were designed for three spinally-injured rabbits. The inputs of the model were from the final ECoG data $z_i(t)$ and the outputs were the intra-spinal stimulation data that were delivered punctually to the detected modules. These went through the following layers: first, through input nodes, which was the collection of ECoG data recorded over time; then, they were coded in the hidden nodes, and finally, the intra-spinal stimulation data were decoded from the ECoG data according to the Equations 3 and 4.

$$3. U_n(t)=f_1 \sum_{10}^{i=1} \sum_{k=0}^{n_x} A_{ni}(k)\, z_i(t-T-k) - \sum_{j=1}^{3} \sum_{k=0}^{n_y} B_{nj}(k)\, y_j(t-T-k)+b_{1n})\ n=1\ to\ 8\ (or\ 6\ or\ 10)$$

$$4.\ y_j(t)=f_2 \sum_{n=1}^{m} C_{jn}\, U_n(t)+b_{2j})\ j=1\ to\ 3$$

Where, $U_n(t)$ shows the output of the n^{th} node in the hidden layer, n_1 is the number of the hidden node, $y_j(t)$ is the predicted stimulation signals delivered to the j^{th}

motor module at the time "t", and are the number of input and output delays, respectively, T is the number of constant delays, z_i(t-T-k) is the i^{th} ECoG feature, (z_i), y_j (t-T-k) is j^{th} stimulation signal predicted by the NARX model at time lag m+k, and A_{ni}, B_{nj} and C_{nj} are respectively the weight vectors for z_i, y_j and U_n. Also, b_{1n} and b_{2j} are the bias weights for hidden and output layers. f_1 and f_2 are the activation function in hidden and output layers. Additionally, j ranges from one to three (the module for three movements) and i ranges from one to ten (2 of ECoG channels *5 of frequency bands).

The main components of the NARX neural network are network architecture and learning algorithms. The network architecture consisted of the number of input delays (nx), the number of output delays (ny), and the number of hidden nodes and type of activation function. With respect to the input (ECoG signal) and output (Intra-spinal electric stimulation) delays, each delay referred to the 20 msec period before sampling. For this purpose, 1 to 20 delays were tested, which corresponded to 20 sampling from ECoG and intra-spinal electric stimulation at every 20 msec. Constant delays (T) were tested at 50, 100, 150, 200, 250, and 300 msec, which was the time before the first ECoG sampling. From up to 20 nodes tested in the hidden layer, a sufficient number of nodes was chosen to explain the relationship between the input and output layer data. The mentioned samples were given to the different learning MATLAB built-in algorithms having varying numbers of nodes, from which the best possible one was chosen to explain the relationship between ECoG and intra-spinal stimulation data. In addition, different activation functions were tested on the data for the hidden and output layers. Similarly, the best possible function was chosen. We verified the validity of the previously defined NARX modes using 10-fold cross-validation (Liu et al., 2017). Firstly, The ECoG final data and corresponding intra-spinal stimulating data were divided randomly into ten segments, which were then used for training and testing the NARX model. For this, the first none segments were used in the training phase, and then in the test phase, the developed NARX model was tested by the remaining segment (i.e. the tenth segment) and the intra-spinal stimulation response in the segment was predicted. Again the process was repeated by using segments two to ten for training the NARX model and testing the developed model based on the first segment data. The process repeated ten times and each segment's data were taken to test the developed NARX model. In each step, NRMS (Equation 1) and CC were calculated for every single segment and their results were summed up. Based on Equation 1, y^p and y^a are the predicted NARX output and the actual intra-spinal stimulating data related to three types of movements, respectively.

Intra-spinal cord stimulation based on the decoded commands extracted from ECoGs in the sedated SCI animal

The developed NARX model was tested in an SCI rabbit for the online condition. In online condition, simultaneous changes in the ECoG signals, intra-spinal stimulation data, and leg joint movements were analyzed in a sedated spinally-injured animal. The ECoG signals for the sedated animal after SCI induction were inputted to the developed NARX model and intra-spinal stimulation related to ECoGs was delivered to the modules. The movements based on predicted intra-spinal stimulation were recorded. The movements were also compared to movements recorded before SCI.

Data analysis

Data analysis and processing were performed by MATLAB software, version 2011a using digital signal processing and statistical analysis toolbox at a significance level of 5%. The fuzzy controllers and NARX models were developed by using the fuzzy logic and neural network toolbox. The online data acquisition and processing were implemented by simulink, real-time workshop, and real-time windows target.

3. Results:

Fuzzy control induced-leg movements in SCI rabbits strongly matched those of healthy ones

An example of joint angles (hip, knee, and ankle) changes in each rabbit (before (healthy condition) and after SCI (induced by the fuzzy control), both under anesthesia) is given in Figure 3. Overall, joint angles of SCI and healthy rabbits were comparable, reflecting that the fuzzy control system could simulate natural leg movements. Three types of movements were successfully restored by fuzzy control for all the leg joints. These movements lasted 0.46±0.24 seconds for pushing the leg toward the back, 0.53±0.23 seconds for pulling the leg into the abdomen, and 0.41±0.19 seconds for pushing the leg forward, which matched those observed for natural movements in healthy animals.

Next, the single movements were repeatedly induced to restore the whole jumping movement using the fuzzy control system. Figure 4 shows the simulated movements produced by electric stimulations delivered to the motor

Table 1. The results of spinal cord stimulation in three types of leg movements produced by the fuzzy controller

Types of Leg Movement		Mean±SD		
		Pushing Leg to the Back	Pulling Leg to Abdomen	Pushing Leg Forward
Hip	K_{hip}		0.34±0.04	
	Joint angle range	82.33±2.46-92.66±2.17	81.22±3.22-91.66±3.08	81.18±2.75-93.33±2.07
	CC	0.71±0.16	0.72±0.20	0.69±0.18
	NRMS	0.26±0.16	0.25±0.12	0.29±0.14
Knee	K_{Knee}		0.46±0.06	
	Joint angle range	94.33±4.24-111±3.96	91.33±2.33-114±2.13	95.66±4.11-110.33±2.38
	CC	0.70±0.24	0.73±0.16	0.70±0.13
	NRMS	0.27±0.11	0.25±0.09	0.28±0.11
Ankle	K_{Ankle}		0.19±0.04	
	Joint angle range	108.21±2.14-118.33±1.94	105.79±1.59-114±2.44	109.33±1.76-113.63±1.88
	CC	0.70±0.17	0.72±0.19	0.71±0.21
	NRMS	0.29±0.09	0.25±0.11	0.25±0.09

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a K_{hip}, K_{Knee} and K_{Ankle} are constant coefficients to normalize the error of the joint angles (hip, knee, ankle). All data are shown as Mean±SD.

Table 2. The optimum architect and predictive performance of the three NARX model

NARX model [a]		Mean±SD		
		Rabbit 1	Rabbit 2	Rabbit 3
Delays in the input layer (n_x)		3	4	3
Hidden layer nodes		8	6	10
Activation function in the hidden layer		Sigmoid	Sigmoid	Tansig
Delays in the output layer (n_y)		3	3	2
CC	Module 1_b	0.77±0.13	0.77±0.11	0.80±0.14
	Module 2_c	0.72±0.17	0.78±0.14	0.78±0.14
	Module 3_d	0.75±0.16	0.75±0.13	0.76±0.14
NRMS	Module 1	0.21±0.08	0.24±0.07	0.23±0.07
	Module 2	0.22±0.11	0.25±0.09	0.21±0.08
	Module 3	0.23±0.08	0.23±0.11	0.22±0.10

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[a] In all NARX models, the activation function in the output layer and learning algorithm was linear (pureline) and Levenberg-Marquardt, respectively. The constant time delay was also considered as 100 ms. [b-d]: Predicted intra-spinal stimulations for modules related to pushing the leg toward the back, pulling the leg into the abdomen, and pushing the leg forward (Mean±SEM of 10 trials, i.e. 10-fold cross-validation for each model).

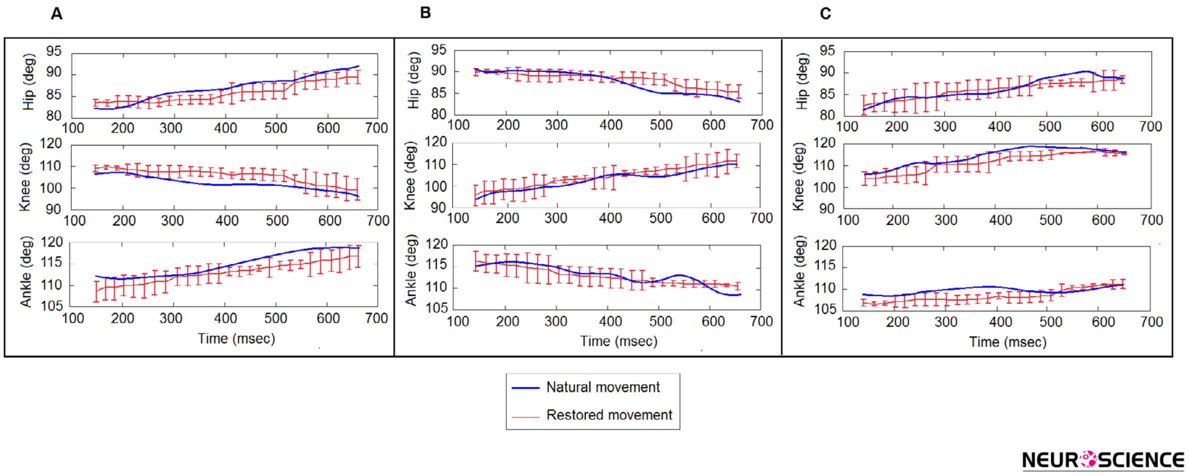

Figure 3. The changes in joint angles observed in natural leg movements before the spinal injury

A, B and C) Show these changes during pushing the leg to the back, pulling the leg to the abdomen, and pushing the leg forward, respectively.

Data are shown as Mean±SEM (n=10).

modules in the spine with the help of the fuzzy controller. Table 1 summarizes the results of spinal cord stimulation in three types of leg movements by the fuzzy controller. Similar to the single movement, it was found that the simulated movements perfectly followed those observed in natural rabbits jumping with respect to three types of leg movements. Three cycles of combined movements were achieved in response to the stimulations' patterns. The acquired response (i.e. movements angles) of the three rabbits was almost within the same range (Table 1); in this regard, the hip joint angle changes for pulling the leg into the abdomen ranged from 81.22±3.22 to 91.66±3.08 with around 3% deviation from the mean. These movements were governed by the fuzzy controller with weighted constant coefficients (K; for different joints: K_{hip}, K_{knee}, and K_{ankle}), which normalized the errors of the angles. Using this system, the restored movement fitted the natural leg movement of the healthy rabbits, evidenced by high CC (about 0.70) but low NRMS errors (about 0.2) confirming a strong correlation between the acquired simulated movements' and natural movements data. Our t-test analysis indicated no remarkable difference in joint angle changes between the SCI and the healthy rabbits.

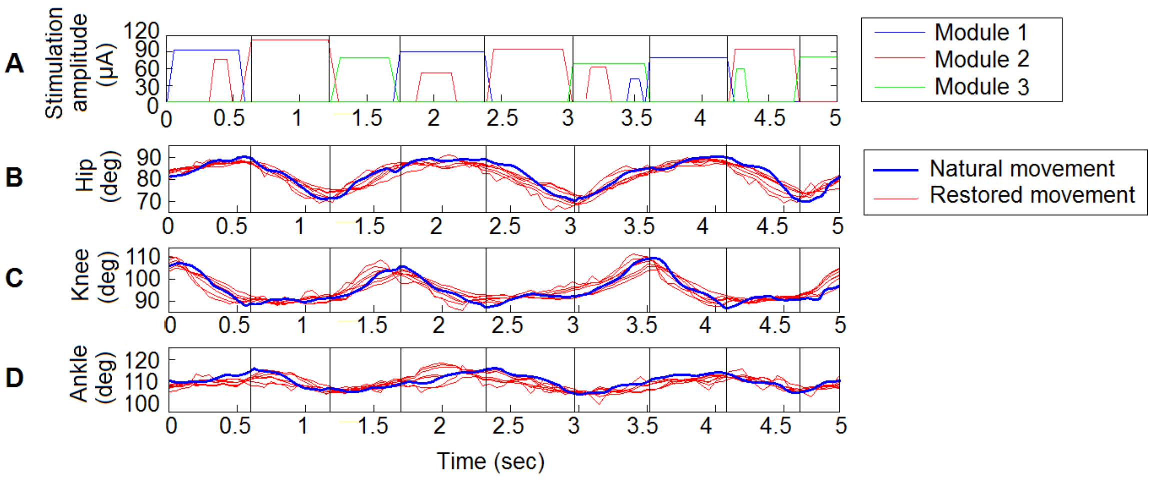

Figure 4. Three simulated movements produced by electric stimulations were delivered to the motor modules in the spine using the fuzzy controllers

A) Shows the electric stimulation patterns for the specific modules; B, C, and D) Illustrate the corresponding three rounds of hip, knee, and ankle joints' movements, in response to the electric stimulations, respectively.

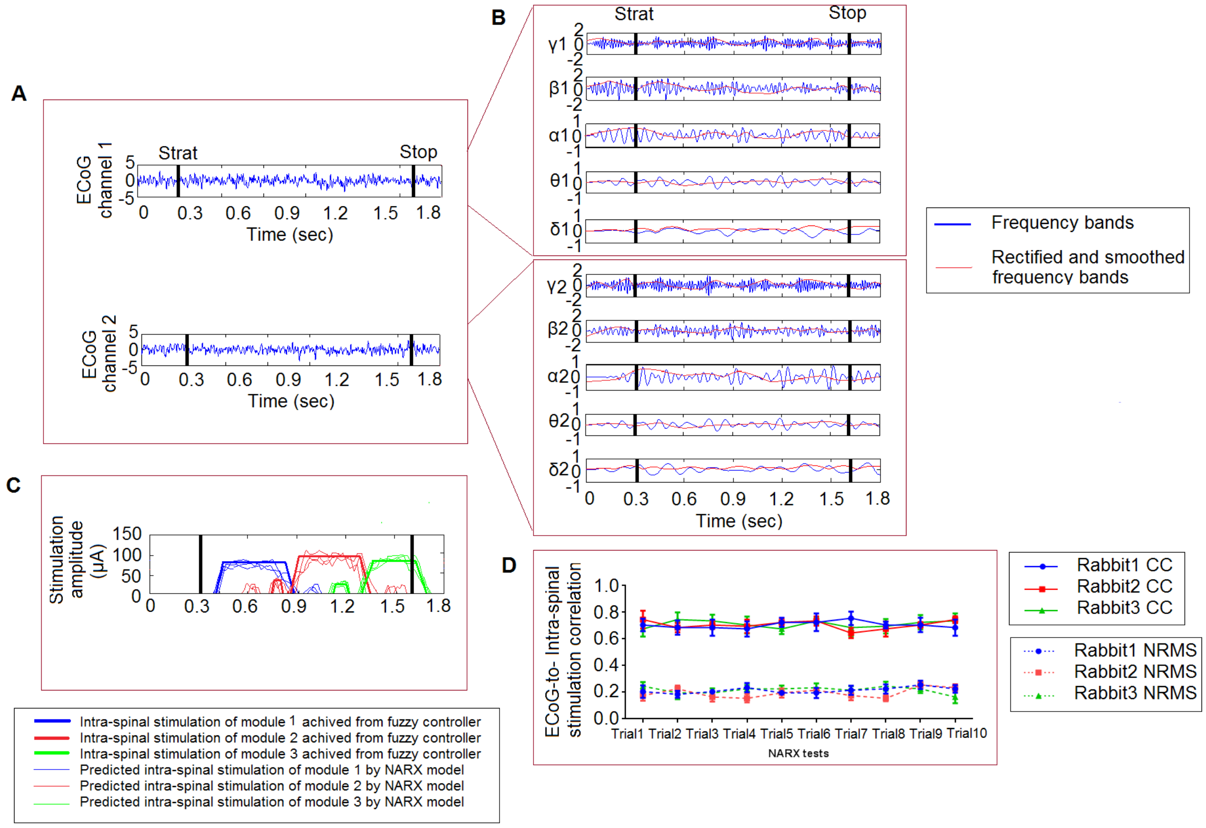

Figure 5. The simulation of ECoG signal-to-intra-spinal relation according to the NARX model NEUROSCIENCE

A) Shows the raw ECoG data obtained from the healthy rabbit (i.e. before spinal injury), where the start and stop points were taken for analysis; B) Shows five frequency bands and also digitally rectified and smoothed signals; C) Illustrates the intra-spinal stimulation signals achieved from the NARX outputs and the intra-spinal stimulation signals achieved from the fuzzy controller; D) Illustrates the total correlation of ECoG to the intra-spinal data in three rabbits as recorded in 10 test trials, as well as the NRMS associated with these relations.

Data are shown as Mean±SEM (n=30) for each trial.

Development of the NARX model

An optimum NARX model capable of deciphering ECoG data to produce intra-spinal stimulations was developed through multiple steps (Table 2). In the first step, the appropriate constant time delay was attained (100 msec). Then, the suitable number of input and output delays were achieved for each rabbit (n_x=3, n_y=3 for model 1, n_x=4, n_y=3 for model 2, and n_x=3, n_y=2 for model 3). After that, it was found that about six to ten hidden nodes were sufficient in this algorithm. The activation function of these nodes was sigmoid type in two rabbits and hyperbolic tangent sigmoid in the third one. Also, linear activation function was considered in output layer for all models. Finally, the learning algorithm of Levenberg-Marquardt was taken from the built-in algorithms in MATLAB software.

Off-line evaluation of the acquired NARX model

The offline evaluation of the acquired NARX model was carried out by testing the model ten times based on the ECoG data achieved in "Simultaneous ECoG and leg kinematics in a sedated healthy animal". These outcomes were compared with intra-spinal stimulation data achieved by the fuzzy control.

Based on our data, the Mean±SD of CC and NRMS error for three rabbits (ten trials each) were 0.75±0.15 and 0.23±0.10 (for the first module), 0.76±0.12 and 0.22±0.08 (for the second module), 0.73±0.15 and 0.22±0.09 (for the third module). Here, CC was 0.74±0.15, and NRMS error was 0.22±0.10. This model was able to produce in-

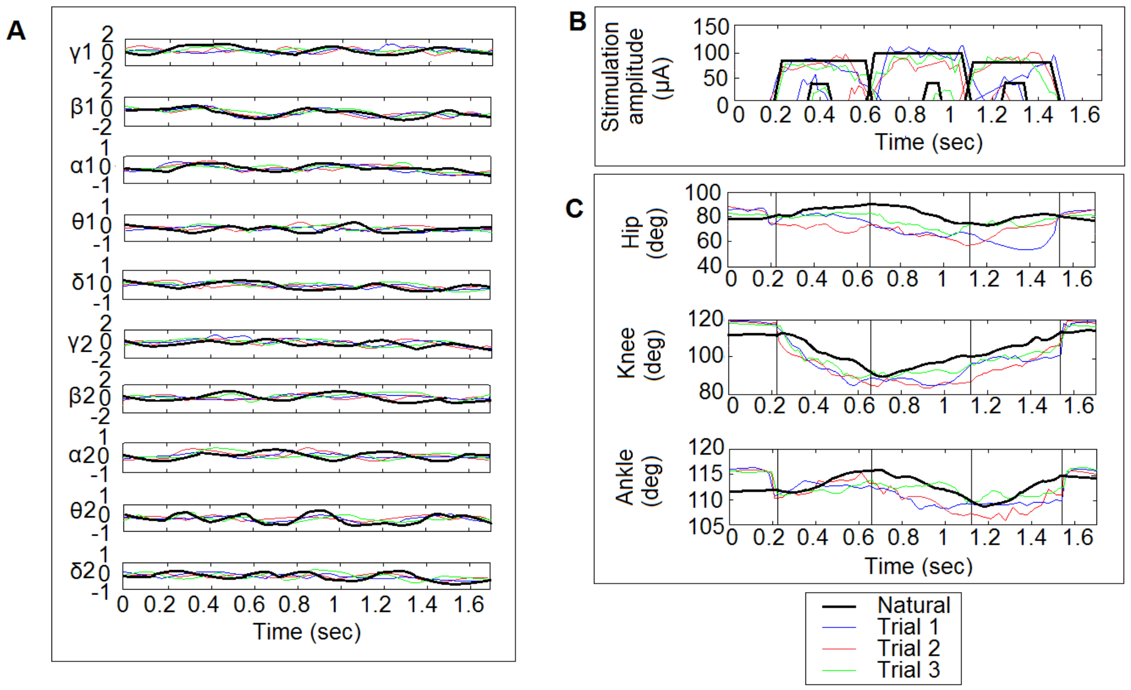

Figure 6. On-line leg movements restoration in a spinally-injured animal using the NARX model

A) Illustrates five ECoG bands in two channels at the time of leg movement in three trails; B) Shows the intra-spinal stimulation amplitude predicted by the NARX model and induced by fuzzy controllers; C) Shows the hip, knee, and ankle joint changes associated with these intra-spinal stimulations and ECoG signals.

tra-spinal stimulations that matched ECoG signals' data at an acceptable level (Table 2).

Figure 5 shows the simulation of the ECoG signal-to-intra-spinal relation according to the NARX model. The intra-spinal stimulation developed using the ECoG information fitted the intra-spinal stimulation data achieved by the fuzzy control (Figure 5 C). Additionally, overall CC and NRMS values revealed a robust relationship between the NARX model predicted outputs and those of the fuzzy control (Figure 5 D). The CC outcome in different trials was above 0.7, denoting a strong correlation. In this regard, the NRMS was about 0.2, which indicates a minimal level of error in the prediction.

On-line evaluation of the acquired NARX model

As shown in Figure 6, the ECoG signal data related to the defined leg movement were similar to those of the non-injured rabbit recorded during the leg movement (Figure 6 A). These ECoG signals almost matched intra-spinal electric stimulation data (Figure 6 B), which finally produced the three types of movements (Figure 6 C). Overall, CC and NRMS values for the online prediction performance of NARX were 0.65±0.12 and 0.33±0.09, respectively. Of note, leg movements produced under the NARX model, to some extent, matched the natural leg movements when the animal was not paralyzed. The CC was 0.61±0.08 and the NRMS tracking error for joint angles was 0.37±0.11 in the online experiment

4. Discussion

In our study, the fuzzy control and NARX system were used in a different way compared to previously published similar attempts. In this context, previously, a fuzzy control and lag compensator was used to control the movement of one joint (i.e. ankle) through intra-spinal stimulation (Roshani et al., 2013). Besides, the NARX model was used for rehabilitation purposes by correlating electroencephalography-to-muscle movement (Liu et al., 2017; Shakibaee et al., 2019). Nevertheless, we correlated the ECoG signal to the intra-spinal electric stimulation based on the presumption that the remnant neural system in the spinal cord down the injured area, could govern the leg movements. It should be noted that the present work was conducted in continuation of our previous works (Heravi et al., 2020a; Heravi et al., 2020b) in spinally injured rabbits. Previously, we used a brain-spine neural interface based on a SLiR model and trial-and-error stimulation for leg movement restoration

(Heravi et al., 2020a). In another study, we employed the SLiR model but used closed-loop fuzzy control, which led to improvement in the leg restoration outcomes and we found it less time-consuming (Heravi et al., 2020b). Nevertheless, in the present work, we used a nonlinear model, which is unlike the SLiR model that is a linear model; this resulted in better prediction of intra-spinal stimulation and enhanced leg restoration results compared to our previous works (Heravi et al., 2020b).

The present system indeed predicted the leg movement based on the brain ECoG signals and then, applied the retrieved information to generate spinal electric signals down the affected region. The electric signal delivered to three detected motor modules eventually induced leg movements similar to those recorded prior to SCI induction. In general, the model successfully rehabilitated the paralyzed rabbit, but, occasionally, the induced leg movement's slightly varied from the natural movements in three maneuvers.

This approach was beneficial for the paralyzed animals; however, some limitations existed. The arbitrary leg movement with the help NARX system and the closed-loop fuzzy control may eliminate the need for constant physiotherapy for the prevention of muscle atrophy and joint stiffness in spinally-injured cases. However, the leg maneuver restored in the present work was far from the ideal leg movement. First of all, the results of the online restored movements indicated that ECoG data partly correlates with the electric spinal stimulus, as shown by the medium level of correlation (0.61±0.08). This emphasizes the complexity of the neural system and the brain-to-muscle movement relationship. Besides, we used three modules detected in the animals' spine, while under real-life conditions, the number of these modules is supposedly markedly higher. It is postulated that by increasing the number of motor modules, a higher precision in terms of leg movement correlated to the ECoG data, could be achieved, which merits investigation. Secondly, the technique still needs to be improved as the strength and speed of the movement are important factors, which were not studied in our study. In this regard, the exploitation of sufficiently higher motor modules down the affected region in the spinal cord may induce leg movements that could lift and hold the body in a natural way.

Under offline conditions, the series-parallel NARX model was used. This structure was used because the true past values of signals were available. In online assessments, the parallel NARX neural network was performed. This approach can be helpful for prediction before online applications. In addition, we achieved the best NARX model and the fuzzy control system through a trial and error approach with constant time delay. In this regard, other logical approaches, like genetic algorithms rather than trial and error, may lead to an improved NARX model, which can explain the relationship between brain signals and leg movement under an electric stimulus. Another issue was the constant time delay used in the development of the NARX model, which might be different for each movement. As a result, the application of variable time delays is worth investigating. As a limitation of the present work, it should be emphasized that the present findings are translatable for anesthetized conditions, and future studies are needed to be conducted also in awaking animals to record the brain signals before SCI induction and apply them in injured animals for restoration of leg movements.

5. Conclusion

Thus, the results of the present study showed that the fuzzy-based intra-spinal stimulation and the developed NARX model could restore leg movements. Using NARX, appropriate information from ECoG recordings can be extracted and used for the generation of proper intra-spinal electric stimulations for restoration of natural leg movements lost due to SCI.

Ethical Considerations

Compliance with ethical guidelines

All experimental procedures were done in compliance with national guidelines for in vivo experiments. The present research was approved by the Ethics Committee of North Khorasan University of Medical Sciences (Code: IR.NKUMS.REC.1400.036).

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Authors' contributions

Conceptualisation: Fereidoun Nowshiravan Rahatabad and Keivan Maghooli; Data collection: Ramin Rezaee and Mohamad Amin Younessi Heravi; Data analysis: Mohamad Amin Younessi Heravi and Keivan Maghooli; Writing the paper: Ramin Rezaee and Mohamad Amin Younessi Heravi.

Conflict of interest

The authors declared no conflicts of interest.

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